EXHIBIT 1, Tab 15

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EDITORIALS

COMMENTARY

ORIGINAL INVESTIGATIONS

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Treatment of Active Rheumatoid Arthritis With Leflunomide Compared With Placebo and Methotrexate

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Context: Leflunomide is a reversible inhibitor of de novo pyrimidine synthesis shown to be effective in a phase 2 trial in 402 patients with active rheumatoid arthritis (RA).

Objective: To compare the efficacy and safety of leflunomide treatment with placebo and methotrexate treatment in patients with active RA.

Design: Randomized, double-blind, placebo, and active-controlled 12-month study.

Setting: Forty-seven university and private rheumatology practices in the United States and Canada.

Patients: Diagnosis of RA by the American College of Rheumatology (ACR) criteria for duration of 6 months or longer and no previous methotrexate treatment.

Intervention: Leflunomide treatment (20 mg/d), placebo, or methotrexate treatment (7.5-15 mg/wk).

Main Outcome Measures: American College of Rheumatology success rate (completed 52 weeks of treatment and met the ACR ≥20% response criteria), disease progression as assessed by x-ray films, and improvement in function and health-related quality of life using the intent-to-treat population.

Results: The 482 patients studied were predominantly women (mean age, 54 years; mean disease duration, 6.7 years) for whom a mean of 0.8 disease-modifying antirheumatic drugs had failed. The ACR response and success rates for patients receiving leflunomide treatment (52% and 41%, respectively) and methotrexate treatment (46% and 35%, respectively) were significantly higher than those for patients receiving placebo (26% and 19%, respectively) ($P<.001$), and they were statistically equivalent, with mean time to initial response at 8.4 weeks for patients receiving leflunomide vs 9.5 weeks for patients receiving methotrexate therapy. X-ray analyses demonstrated less disease progression with leflunomide ($P\leq.001$) and methotrexate ($P = .02$) therapy than with placebo. Leflunomide and methotrexate treatment improved measures of physical function and health-related quality of life significantly more than placebo ($P<.001$ and $P<.05$, respectively). Common adverse events for patients receiving leflunomide treatment included gastrointestinal complaints, skin rash, and reversible alopecia. Asymptomatic transaminase elevations resulted in treatment discontinuations for 7.1% of patients receiving leflunomide therapy, 1.7% of patients receiving placebo, and 3.3% of patients receiving methotrexate therapy.

Conclusions: Clinical responses following administration of leflunomide, a new therapeutic agent for the treatment of RA, were statistically superior to those with placebo and equivalent to those with methotrexate treatment. Both active treatments improved signs and symptoms of active RA, delayed disease progression as demonstrated by x-ray films, and improved function and health-related quality of life.

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The affiliations of the authors appear in the acknowledgment section at the end of the article; a complete list of the Leflunomide Rheumatoid Arthritis Investigators Group appears on page 2549.

CURRENT treatments for rheumatoid arthritis (RA) include nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose steroids, and disease-modifying antirheumatic drugs (DMARDs). The active control drug for this study, methotrexate, is considered to be the "gold standard" DMARD for the treatment of RA.[1-4] No currently available medication is uniformly effective, however, and all may cause significant adverse effects.[5]

Leflunomide is an isoxazole immunomodulatory agent with demonstrated prophylactic and therapeutic effects in animal models of autoimmune disease.[6] Following oral administration of leflunomide, the isoxazole ring is rapidly cleaved to form the active metabolite, which binds to the enzyme dihydroorotate dehydrogenase, thereby inhibiting de novo pyrimidine synthesis.[7] In rapidly dividing cell populations, such as activated lymphocytes, this results in cell cycle arrest, which can be reversed in vitro and in vivo by the administration of uridine.[8,9]

PATIENTS AND METHODS

PATIENT POPULATION

Men and women aged 18 years or older were eligible for treatment if they met the American College of Rheumatology (ACR) criteria for having RA for 6 months or longer.[11] Active RA was defined by 3 of the following 4 criteria: 9 or more tender joints, 6 or more swollen joints, morning stiffness lasting 45 minutes or longer, and Westergren erythrocyte sedimentation rate (ESR) of 28 mm/h or greater. Notably, patients could not have previously received methotrexate treatment; treatment with all other DMARDs must have been discontinued for at least 30 days. Prednisone treatment (≤10 mg/d) (or the equivalent) and NSAIDs were permitted if dosages had been stable for at least 30 days before enrollment and remained stable during treatment. Patients were excluded if they had inflammatory joint disease that was not caused by RA, had a history of clinically significant drug or alcohol abuse, or admitted to consumption of more than 1 alcoholic drink per day. Required baseline laboratory values included a hemoglobin concentration of 100 g/L or greater; a hematocrit of 0.30 or greater; a leukocyte count of 3×10^9/L or greater; a platelet count of 100×10^9/L or greater; a serum creatinine level lower than twice the upper limit of normal (ULN) for age and sex; an albumin level greater than or equal to the lower limit of normal (≥35 g/L); and normal liver function test results, defined as 3 or more serial evaluation results that were less than or equal to 1.2 times the ULN for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and bilirubin levels. Sexually active premenopausal women and men were instructed to use a medically accepted form of contraception throughout treatment and for 6 months thereafter.

STUDY PROTOCOL

This was a randomized 12-month multicenter double-blind placebo-controlled study designed in 1993 and initiated (with regulatory approval) in 1995. All patients gave informed consent and then provided a medical history and underwent physical examination, laboratory assessment, chest x-ray, and electrocardiography. Baseline clinical assessments included tender and swollen joint counts (28 joints), patient and physician global assessments of disease activity (on a visual analog scale [VAS], 0-100 cm), patient assessment of pain (VAS, 0-100 cm), Modified Health Assessment Questionnaire (MHAQ) score,[12] Westergren ESR, and C-reactive protein (CRP) level. Rheumatologic assessments were performed biweekly during weeks 4 through 12 and monthly thereafter. The Health Assessment Questionnaire (HAQ), Problem Elicitation Technique (PET) questionnaire (a disease-specific instrument that asks patients to identify and rank activities most affected by their RA), and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) were completed by patients at baseline and at 24 and 52 weeks of treatment or at the time of study exit.[13-15] Radiographs of the hands and feet were taken at baseline and at 52 weeks or at the time of early study exit, using fine-grained, single-emulsion film and following protocol specifications for optimal positioning.[16] The ACR response criteria were used, which required improvement of 20% or greater in both tender and swollen joint counts as well as improvement of 20% or greater in 3 of the following 5 measures: patient self-assessed function/disability (MHAQ), patient global assessment, physician global assessment, patient assessment of pain, and acute-phase reactant value assessed by ESR or CRP level.[17] The ACR response rates for improvement of 50% and greater and 70% and greater were also calculated.

TREATMENT ASSIGNMENT

Patients were assigned to 1 of 3 treatment groups in a 3:2:3 randomization: leflunomide treatment (20 mg/d), placebo, or methotrexate treatment (7.5 mg/wk). Patients were enrolled in the order of confirmed eligibility. Randomization was stratified according to the time since the patient's last treatment with a DMARD (<8 or ≥8 weeks). Study sites obtained unique patient numbers by calling a randomization center, which used a computerized adaptive algorithm to assign treatment based on stratum and, to maintain balance, the number of patients previously assigned at that site to each arm. To preserve the blind, all patients received an oral dose of leflunomide or matching leflunomide placebo once daily and an oral dose of methotrexate or matching methotrexate placebo once per week.

A daily 20-mg dose of leflunomide was selected based on the phase 2 efficacy and pharmacokinetics data. Based on the 14- to 16-day half-life of the active metabolite, a 100-mg loading dose of leflunomide or leflunomide

Continued on the next page

Leflunomide treatment was reported to be effective at dosages of 10 and 25 mg daily in a 6-month phase 2 study of 402 patients with active RA.[10] This article describes a 12-month double-blind phase 3 study designed to provide long-term data on the safety and efficacy of leflunomide treatment compared with placebo and methotrexate therapy for patients with active RA.

RESULTS

PATIENT CHARACTERISTICS

Of 485 patients enrolled at 42 sites, 482 received at least 1 dose of a study drug or placebo and were evaluated for safety; 480 had at least 1 follow-up visit to evaluate efficacy (182 patients received leflunomide therapy, 118 received placebo, and 180 received methotrexate therapy [3:2:3 randomization]). Demographic and disease characteristics were similar across treatment groups (**Table 1** and **Table 2**). Two hundred thirty-eight patients completed 52 weeks of initial treatment (leflunomide therapy, 53%; placebo, 31%; and methotrexate therapy, 58%); 108 of 132 eligible patients received alternate therapy (leflunomide therapy, 13%; placebo, 44%; and methotrexate therapy, 18%). In total, 346 patients completed protocol treatment (leflunomide therapy, 66%; placebo, 75%; and methotrexate therapy, 77%). Early discontinuations occurred more often with placebo (69%) than with leflunomide (47%) or methotrexate (42%) therapy. These discontinuations were caused by a lack of efficacy in 53% of patients receiving placebo compared with 17% of patients receiving leflunomide and 24% of patients receiv-

placebo was administered for the first 3 days to allow a steady-state plasma concentration to be reached within 6 to 8 weeks. Consistent with current medical practice, all patients received 1 mg of folate once or twice daily. If active disease (as defined above) was still present at week 6 of protocol treatment, the methotrexate or methotrexate placebo dosage was mandated to be increased to 15.0 mg over weeks 7 through 9 and continued thereafter.

If a patient's response failed to meet the ACR response criteria after 16 weeks of treatment or if a patient developed an unacceptable adverse event, the initial study medication could be discontinued and, after a washout period, the patient could elect to receive alternate therapy. Patients who chose alternate therapy and were originally assigned to methotrexate therapy or placebo received leflunomide therapy; those who were originally assigned to leflunomide therapy received methotrexate therapy. Allocations to initial and alternate therapy were done at the time of study entry and remained blinded. This report presents results from the initial therapy phase only.

Consistent with the recommended ACR guidelines for monitoring methotrexate therapy, dosage adjustments, discontinuation of treatment, and/or liver biopsies were mandated for persistent or recurrent transaminase elevations.[18] For elevations that were greater than twice the ULN, daily and weekly medication dosages were reduced; for elevations that were greater than 3 times the ULN or repetitive elevations that were greater than twice the ULN despite dosage reduction, initial therapy was discontinued.

STATISTICAL ANALYSES

The principal objective of the study was the comparison of leflunomide therapy with placebo. Comparisons of leflunomide therapy with methotrexate therapy and methotrexate therapy with placebo were secondary objectives of the study; therefore, *P* values are reported without adjustment. The primary measure of efficacy was meeting the ACR 20% response criteria and completing 52 weeks of initial therapy (ACR success). The ACR response rates for improvement of 50% or greater and 70% or greater at 12 months were also determined. Secondary outcome measures included mean changes over time in each of the components of the ACR response criteria, results of hand and feet x-ray films, measures of physical function and health-related quality of life (assessed with the HAQ, PET questionnaire, and SF-36), duration of morning stiffness, and rheumatoid factor titers.

In accordance with the US Food and Drug Administration final guidance document for the clinical development of drugs, devices, and biologic agents for the treatment of RA, the retardation of disease progression as demonstrated by x-ray evaluation and improvement in function and health-related quality of life represent potential claims only if the primary end point shows a statistically significant difference.[19] Therefore, these analyses were conditioned on the primary analysis and no multiple comparison adjustment was required.

Original sample size requirements were determined based on 4 primary variables: tender joint count, swollen joint count, physician global assessment, and patient global assessment. Later calculations that were performed after the study had begun confirmed that the estimated sample size would be sufficient to demonstrate treatment differences using the ACR response criteria. This sample size provided a 90% power to detect treatment differences.

All efficacy statistical analyses were performed on the intent-to-treat population, defined as all randomized patients who received any dosage of study medication with at least one study evaluation after randomization. In addition to descriptive statistics, comparisons of on-treatment values with baseline values for the 3 treatment groups used logistic regression analysis for categorical variables and analysis of covariance for continuous variables. Analyses used the last observation carried forward method. As health-related quality-of-life data were not normally distributed at baseline, the van Elteren extension to the Wilcoxon rank sum test results was applied to continuous variables, and the Cochran-Mantel-Haenszel χ^2 test results were applied to categorical variables comparing change from baseline.

Statistical analyses (analysis of covariance for 95% confidence intervals and *P* values) included comparisons and possible interactions using duration of disease ($\leq$2 or $>$2 years), no prior DMARD therapy, concomitant corticosteroid and/or NSAID administration, investigator pool, geographic region, and recent DMARD therapy ($\leq$8 or $>$8 weeks). The analysis plan defined 5 geographic regions for the investigational sites.

Reports of adverse events, physical examination results, standard laboratory assessments, electrocardiogram results, and chest x-ray results were analyzed for safety, including mean changes in individual parameters over time.

ing methotrexate therapy. The number of treatment withdrawals increased most notably in the placebo group on or after the 4-month visit, at which time entry into alternate therapy was allowed (**Figure 1** and **Table 3**).

The weekly dosage of methotrexate was increased to 15 mg for 109 patients (61%) receiving methotrexate therapy. Increased dosages of methotrexate placebo were mandated for 95 patients (52%) receiving leflunomide therapy and 81 patients (69%) receiving placebo. Dosage reductions occurred in 3 patients (2%) receiving leflunomide therapy, none in the placebo group, and 4 patients (2%) receiving methotrexate therapy. Early withdrawals caused by adverse events occurred in 22% of the patients receiving leflunomide therapy, 10% of the patients receiving methotrexate therapy, and 9% of the patients receiving placebo (**Table 4**). In the leflunomide group, most early withdrawals were caused by gastrointestinal events (5.5%) or protocol-mandated discontinuations for asymptomatic transaminase elevations (7.1%).

COMPARISON OF LEFLUNOMIDE TREATMENT WITH PLACEBO

The ACR success rate was significantly higher in the leflunomide treatment group compared with the placebo group (41% vs 19%; $P<.001$). Mean changes over time in each component of the ACR response index were significantly better in the leflunomide and methotrexate treatment groups than in the placebo group ($P\leq.01$) (Table 2). The ACR response rates over time are shown in **Figure 2**. The data for the area under the response curve (AUC) (the number of weeks a patient reported improvement according to the

Table 1. Demographic and Disease Characteristics*

	Leflunomide (n = 182)	Placebo (n = 118)	Methotrexate (n = 182)
Female, %	72.5	70.3	75.3
Age, y†	54.1 ± 12.0	54.6 ± 10.7	53.3 ± 11.8
Rheumatoid arthritis duration, y†	7.0 ± 8.6	6.9 ± 8.0	6.5 ± 8.1
Rheumatoid arthritis duration ≤2 y, %	39.0	33.3	40.1
Rheumatoid factor positive, %	64.8	60.2	59.4
No. of DMARDs that failed†	0.8 ± 1.0	0.9 ± 0.9	0.9 ± 1.0
No prior DMARD treatment, %	44.5	39.8	44.0
Taking concomitant NSAIDs, %	75.2	65.2	69.7
Taking concomitant steroids, %	53.8	55.1	52.7

*DMARD indicates disease-modifying antirheumatic drug; NSAID, nonsteroidal anti-inflammatory drug.
†Values are mean ± SD.

Table 2. Change in Individual Outcome Parameters for the Intent-to-Treat Population*

	Leflunomide (n = 182)	Placebo (n = 118)	Methotrexate (n = 180)
Joint count (range, 0-28)			
Tender			
Baseline	15.5 ± 6.4	16.5 ± 6.3	15.8 ± 6.9
Mean change	−7.7 ± 7.8†	−3.0 ± 8.4	−6.6 ± 7.6†
Swollen			
Baseline	13.7 ± 6.0	14.8 ± 6.2	13.0 ± 5.7
Mean change	−5.7 ± 6.5†	−2.9 ± 6.1	−5.4 ± 5.5†
Global assessment of disease activity (VAS)			
Patient			
Baseline	5.6 ± 2.2	5.8 ± 2.2	5.4 ± 2.3
Mean change	−2.1 ± 2.7†	0.1 ± 2.8	−1.5 ± 2.9†
Physician			
Baseline	6.1 ± 1.5	6.2 ± 1.6	5.9 ± 1.7
Mean change	−2.8 ± 2.8†	−1.0 ± 2.5	−2.4 ± 2.7†
MHAQ score			
Baseline	0.8 ± 0.6	0.9 ± 0.5	0.8 ± 0.5
Mean change	−0.3 ± 0.5†‡	0.1 ± 0.5	−0.2 ± 0.5§
Patient assessment of pain (VAS)			
Baseline	5.9 ± 2.2	6.4 ± 1.9	5.8 ± 2.2
Mean change	−2.2 ± 2.9†	−0.4 ± 2.4	−1.7 ± 2.8†
ESR, mm/h			
Baseline	38.4 ± 26.8	37.3 ± 28.7	33.8 ± 25.4
Mean change	−6.3 ± 22.9§	2.6 ± 19.0	−6.5 ± 20.6†
CRP, mg/dL			
Baseline	2.08 ± 2.50	2.47 ± 2.67	1.88 ± 1.87
Mean change	−0.62 ± 2.45†	0.47 ± 2.14	−0.50 ± 1.87†

*Values are mean ± SD. VAS indicates visual analog scale (range, 0-100 cm); MHAQ, Modified Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; and CRP, C-reactive protein.
†Leflunomide or methotrexate vs placebo, P≤.001.
‡Leflunomide vs methotrexate, P≤.01.
§Leflunomide or methotrexate vs placebo, P≤.01.

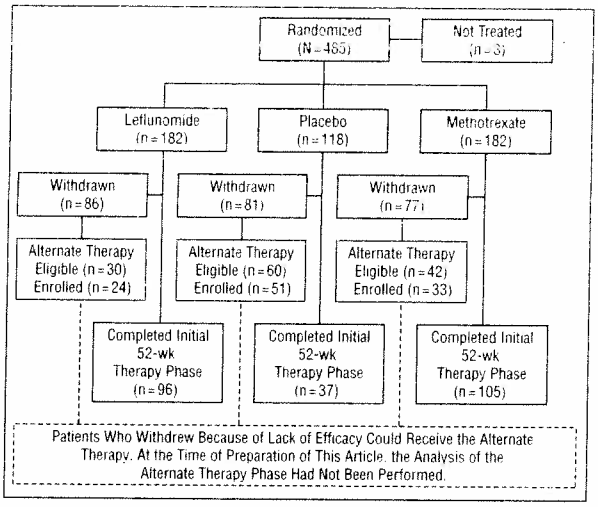

Figure 1. *Study profile. The disposition of all randomized patients is shown for the initial and alternate phases of the study.*

Table 3. Reasons for Study Withdrawals

Reason for Withdrawal	No. of Patients: Leflunomide (n = 86)	Placebo (n = 81)	Methotrexate (n = 77)
Adverse event*	40	10	19
Lack of efficacy	31	62	44
Protocol violation	0	1	1
Noncompliance	1	0	1
Lost to follow-up	1	0	2
Voluntary	11	8	10
Other	2	0	0

*Includes 1 death in the methotrexate group.

Table 4. Adverse Events Leading to Treatment Withdrawal

Adverse Event	Patients Withdrawn, %: Leflunomide (n = 182)	Placebo (n = 118)	Methotrexate (n = 182)
Total	22.0	8.5	10.4
Elevated transaminase level	7.1	1.7	4.4
Gastrointestinal	5.5	1.7	1.7
Rash	2.2	2.5	0.0
Hypertension	1.1	0.8	0.0
Hyperlipidemia	1.6	0.0	0.0
Myocardial infarction	0.5	0.0	0.5
Pneumonia	0.5	0.0	0.5
Interstitial pneumonitis	0.0	0.0	0.5
Alopecia	0.5	0.8	1.1
Other	3.0	1.0	1.7

ACR criteria), time to and duration of initial ACR response, time to and duration of sustained ACR response (reported improvement according to the ACR criteria at ≥3 consecutive visits [minimum duration, 8 weeks], and ACR response rates [improvement ≥20%, ≥50%, and ≥70%]) are displayed in **Table 5**. American College of Rheumatology

responses in the leflunomide group occurred earlier and exceeded those in the placebo group at all time points.

Radiographs of the hands and feet at baseline and 12 months (and at the time of early exit) were obtained for 352 (73%) of 482 patients. Analyses were based on 12-month x-ray films, except when those taken at the time

of early exit were the only follow-up films available (n = 47). Significantly more disease progression occurred in patients treated with placebo compared with leflunomide therapy and approached the estimated progression (defined as the Sharp score at baseline divided by disease duration at baseline) (**Table 6**).

Analyses of function/disability and health-related quality of life demonstrated statistically significant improvement in patients treated with leflunomide compared with patients who received placebo, not only for the MHAQ, the HAQ disability index, and the physical component score of the SF-36, but for all scales of the HAQ and the weighted top-3 score of the PET questionnaire (**Table 7**).

A geographic analysis of site-to-site variations in responses revealed no significant interactions, and no site enrolled more than 5% of the total patient population. Subanalyses of responses according to disease duration, prior DMARD therapy, and concomitant corticosteroid or NSAID administration indicated no significant differences, with the exception of a better ACR response rate in the placebo population with a disease duration of more than 2 years compared with a disease duration of 2 years or less.

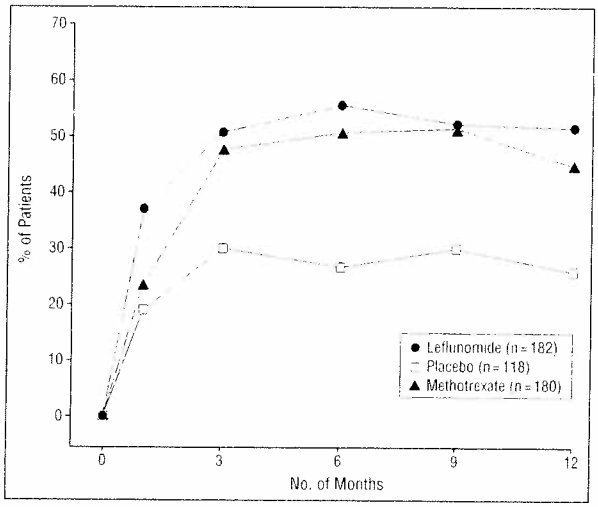

Figure 2. *Intent-to-treat last observation carried forward analysis of the percentage of patients who met the American College of Rheumatology response criteria for improvement of 20% or greater at month 1 and quarterly thereafter by treatment group. P values calculated for the 12-month data are presented in Table 5.*

COMPARISON OF LEFLUNOMIDE WITH METHOTREXATE THERAPY

The ACR success rates in the leflunomide and methotrexate treatment groups (41% and 35%, respectively) were statistically equivalent. Responses from patients receiving methotrexate treatment were significantly better than those for patients receiving placebo. The ACR greater than or equal to 20% response rates over time for patients receiving leflunomide and methotrexate therapy were 52% and 46%, respectively. Onset of effect occurred at a mean of 8.6 weeks for patients in the leflunomide treatment group compared with 9.5 weeks for those in the methotrexate treatment group.

Because increases in the dosage of methotrexate therapy from 7.5 to 15 mg/wk occurred only for patients who had no response to treatment, the ACR success rates did not differ significantly for patients receiving 15 mg/wk vs those whose dosage remained at 7.5 mg/wk (34% and 37%, respectively). This was also true for the leflunomide and placebo groups; the ACR success rates in patients whose dosage of methotrexate placebo was increased were 40% for the leflunomide group and 18% in the placebo group, compared with 42% and 20%, respectively, for those whose dosage was not increased.

Significantly less disease progression by x-ray analysis occurred with methotrexate treatment than with placebo. Results were better for the leflunomide group than for the methotrexate group ($P = .05$). Patients receiving leflunomide therapy reported more improvement than those receiving methotrexate therapy as assessed by the HAQ disability index, weighted top-3 score of the PET questionnaire, 5 scales of the HAQ, and 2 of 8 subscores of the SF-36 (Table 7).

Table 5. Patient Responses According to the American College of Rheumatology Rheumatoid Arthritis Success and Improvement Criteria by Treatment Group for the Intent-to-Treat Population*

Parameter	Leflunomide (n = 182)	Placebo (n = 118)	Methotrexate (n = 182)
Success, % (95% CI)†‡	41 (33.5-47.8)§	19 (11.5-25.7)	35 (29.0-42.0)§
≥20% improvement, % (95% CI)†	52 (45.0-60.0)§	26 (18.0-34.0)	46 (38.0-53.0)§
≥50% improvement, % (95% CI)	34 (27.0-41.0)§	8 (3.0-12.0)	23 (17.0-29.0)§
≥70% improvement, % (95% CI)	20 (14.0-26.0)§	4 (1.0-8.0)	9 (5.0-14.0)
No. of weeks patients reported ≥20% improvement†	23.7 (20.6)§	12.6 (17.1)	22.7 (19.2)
Time to initial response, wk¶	8.6 (7.4)	10.4 (8.6)	9.5 (6.5)
Sustained response, %#	53	34	57
Time to sustained response, wk¶	10.7 (9.3)	14.7 (11.5)	14.0 (10.2)
Duration of sustained response, wk¶	33.4 (16.1)	26.4 (13.6)	29.6 (15.0)

*CI indicates confidence interval.
†According to the American College of Rheumatology criteria for improvement in rheumatoid arthritis.
‡Success was defined as completing 52 weeks of initial therapy, with improvement of 20% or greater at end point.
§Leflunomide or methotrexate therapy vs placebo, P≤.001.
∥Last observation carried forward.
¶Values are mean (SD).
#Improvement of 20% or greater at 3 or more consecutive visits.

Table 6. Mean Changes From Baseline in Total Sharp Scores and Erosion and Joint Space Narrowing Subscores for the Intent-to-Treat Population*

	Leflunomide (n = 131)	Placebo (n = 83)	Methotrexate (n = 138)
Total Sharp score			
Baseline	23.11 (34.0)	25.37 (31.3)	22.76 (39.0)
Estimated yearly progression†	3.30	3.68	3.50
Change at end point	0.53 (4.5)‡	2.16 (4.0)	0.88 (3.3)§
Erosion subscore			
Baseline	8.95 (19.6)	9.28 (14.2)	8.05 (18.4)
Change at end point	0.23 (2.2)¶	0.84 (1.8)	0.48 (1.8)
Joint space narrowing subscore			
Baseline	14.15 (18.9)	16.10 (20.8)	14.71 (23.3)
Change at end point	0.31 (2.8)#	1.24 (2.7)	0.41 (1.8)¶

*All x-ray films were read using the Sharp method (Bluhm et al[16]). Total Sharp scores are the sum of the erosion and joint space narrowing subscores. Values are mean (SD).

†Estimated as the total Sharp score at baseline divided by the mean disease duration at baseline.

‡Leflunomide therapy vs placebo, P≤.001.

§Methotrexate therapy vs placebo, P = .02.

‖Leflunomide vs methotrexate therapy, P = .05.

¶Leflunomide therapy vs placebo, P = .033.

#Leflunomide therapy vs placebo, P<.001.

SAFETY

Serious adverse events that were considered to be treatment-related by the investigator were reported for 2 patients receiving leflunomide therapy, 2 patients receiving placebo, and 5 patients receiving methotrexate therapy. These included asymptomatic transaminase elevations not requiring hospitalization (leflunomide therapy, n = 1; placebo, n = 1; and methotrexate therapy, n = 2); nonfatal sepsis (leflunomide therapy, n = 1; and placebo, n = 1); and 1 death caused by sepsis, 1 case of interstitial pneumonitis, and 1 case of pneumonia in patients who were treated with methotrexate therapy. Withdrawals caused by adverse events occurred more frequently in the leflunomide group than in the placebo or methotrexate groups (Table 4). The higher incidence of withdrawals for patients receiving leflunomide therapy was primarily owing to gastrointestinal complaints and protocol-mandated withdrawals caused by asymptomatic transaminase elevations.

Gastrointestinal complaints, specifically diarrhea, were more commonly reported by patients receiving leflunomide treatment (**Table 8**). Gastroenteritis and oral ulcers were more frequently reported by patients receiving methotrexate treatment. Mild to moderate allergic reactions, predominantly rash and pruritus, were more common in patients receiving leflunomide treatment than in patients receiving methotrexate treatment or placebo; there were no cases of anaphylaxis or angioedema. Infections, predominantly upper respiratory infections, bronchitis, and pneumonia, were most common in patients receiving methotrexate treatment and least common in patients receiving placebo; this was caused in part by the longer protocol exposure times in the active treatment groups. One case of sepsis occurred in each treatment group. No opportunistic infection or case of disseminated herpes was reported. The most frequent cardiovascular adverse event was mild to moderate hypertension, which responded readily to therapy. Hypertension was overrepresented in the leflunomide group at baseline (8.8%, compared with 5.1% for the placebo group and 1.1% for the

Table 7. Mean Changes in Measures of Function/Disability and Health-Related Quality of Life for the Intent-to-Treat Population*†

	Leflunomide	Placebo	Methotrexate
HAQ disability index	(n = 164)	(n = 99)	(n = 168)
Baseline	1.3	1.3	1.3
Mean change at end point	−0.45‡§	0.0	−0.26‡
PET weighted top-5 score	(n = 166)	(n = 101)	(n = 170)
Baseline	21.2	22.4	20.4
Mean change at end point	−6.91‡	−0.66	3.41
SF-36 physical component	(n = 157)	(n = 101)	(n = 162)
Baseline	30.0	28.9	29.7
Mean change at end point	7.6‡	1.0	4.6‖

*The population includes 438 instead of 480 subjects because 4 did not complete a baseline questionnaire (a validated Spanish translation of the SF-36 was lacking at the time this study was started) and because 20 subjects exited early and did not complete follow-up questionnaires; 18 questionnaires were excluded because of inconsistent responses, 9 at baseline and 9 at follow-up, as calculated by the "response consistency index" developed by the Health Institute, New England Medical Center, Boston, Mass.

†HAQ indicates Health Assessment Questionnaire; PET, Problem Elicitation Technique questionnaire; and SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey.

‡Leflunomide or methotrexate vs placebo, and leflunomide vs methotrexate, P≤.001.

§Leflunomide vs methotrexate, P≤.01.

‖Methotrexate vs placebo, P<.05.

Table 8. Summary of Reported Adverse Events

	% of Patients (95% Confidence Interval)		
Adverse Event	Leflunomide (n = 182)	Placebo (n = 118)	Methotrexate (n = 182)
Treatment-related serious adverse events	1.1 (−13 to 16)	1.7 (−16 to 20)	2.7 (−12 to 17)
Withdrawals because of adverse events	22.0 (9 to 35)	8.5 (−9 to 26)	10.4 (−3 to 24)
Total gastrointestinal	60.4 (51 to 70)	41.5 (28 to 55)	51.6 (42 to 62)
Diarrhea	33.5 (22 to 45)	16.9 (1 to 33)	19.8 (7 to 33)
Nausea/vomiting	20.9 (8 to 34)	18.6 (2 to 35)	19.2 (6 to 32)
Abdominal pain	13.7 (0 to 27)	6.8 (−11 to 24)	15.4 (2 to 29)
Dyspepsia	13.7 (0 to 27)	11.9 (−5 to 19)	13.2 (0 to 27)
Gastroenteritis	2.2 (−12 to 16)	1.7 (−16 to 20)	5.5 (−9 to 20)
Oral ulcers	6.0 (−8 to 20)	5.9 (−12 to 23)	9.9 (−4 to 24)
Allergic reactions	24.2 (12 to 37)	14.4 (−2 to 31)	17.0 (4 to 30)
Infections	56.6 (47 to 66)	48.3 (35 to 61)	59.9 (51 to 69)
Hypertension*	11.0 (−3 to 25)	5.1 (−13 to 23)	2.7 (−12 to 17)
New-onset hypertension†	2.1 (−12 to 16)	0	1.6 (−13 to 16)
Alopecia	9.9 (−4 to 24)	0.8 (−17 to 18)	6.0 (−8 to 20)

*Hypertension reported as an adverse event (systolic blood pressure [BP] ≥160 mm Hg and/or diastolic BP ≥90 mm Hg 2 or more times during the treatment phase).

†Patients without either a diagnosis of hypertension at baseline or systolic BP of 160 mm Hg or greater and/or diastolic BP of 90 mm Hg or greater at screening or baseline, prior to treatment.

Table 9. Summary of Transaminase Elevations

	% of Patients		
	Leflunomide (n = 182)	Placebo (n = 118)	Methotrexate (n = 182)
Reported as an adverse event	14.8	2.5	11.5
Withdrawals	7.1	1.7	4.4
ALT level			
2 times ULN and ≤ 3 times ULN	6.6	0	6.6
3 times ULN	4.4	2.5	2.7
Reversible to ≤ 2 times ULN	11.0	2.5	9.3
AST level			
2 times ULN and ≤ 3 times ULN	6.0	1.7	6.0
3 times ULN	2.2	1.7	0.5
Reversible to ≤ 2 times ULN	8.2	3.4	6.5

ALT indicates alanine aminotransferase, AST, aspartate aminotransferase; and ULN, upper limit of normal

methotrexate group). New-onset hypertension occurred in 2.1% of patients receiving leflunomide therapy compared with 0% of patients receiving placebo and 1.6% of patients receiving methotrexate therapy, all of whom were receiving concomitant NSAIDs. Excluding those patients with preexisting hypertension, mean increases in systolic and diastolic blood pressure were mild and similar across treatment groups (leflunomide group, 2.2 and 1.9 mm Hg, respectively; placebo group, 3.0 and 1.2 mm Hg; and methotrexate group, 1.9 and 1.3 mm Hg). Reversible alopecia was reported more frequently with leflunomide treatment than with methotrexate treatment; it caused 1 patient in the leflunomide group, 1 patient in the placebo group, and 2 patients in the methotrexate group to withdraw. Reversible renal failure occurred in 1 patient 29 weeks after beginning methotrexate treatment.

There were no adverse effects on hematologic parameters caused by leflunomide administration. One case of thrombocytopenia (platelet count $<100 \times 10^9$/L) occurred in the methotrexate group. Treatment with leflunomide resulted in elevated ALT and/or AST levels that were greater than twice the ULN in 11.0% of patients, compared with 3.4% in the placebo group and 9.3% in the methotrexate group. In both active treatment groups, ALT levels were affected more frequently than AST levels (**Table 9**). All elevations for patients receiving leflunomide treatment (n = 20) reverted to less than twice the ULN while treatment continued (n = 10) or after treatment discontinuation (n = 10). Mild elevations in alkaline phosphatase levels were infrequent; those elevations that were greater than twice the ULN were not related to treatment but were associated with concurrent illness. Liver biopsies were performed in accordance with ACR guidelines for 2 patients, 1 receiving leflunomide therapy (after 102 weeks) and 1 receiving methotrexate therapy (after 54 weeks); the biopsy specimens showed no evidence of fibrosis.

COMMENT

This study demonstrates that leflunomide treatment results in sustained improvement in the signs and symptoms of RA over a 12-month period: 41% of patients treated with leflunomide fulfilled the ACR success definition and 52% reported improvement of 20% or greater in accordance with the ACR response criteria—results that were statistically equivalent to those for patients receiving methotrexate treatment (33% and 46%, respectively) and superior to those for patients receiving placebo (19% and 26%, respectively). Mean changes over time in all components of the ACR response index were significantly better for patients in the active treatment groups than for patients receiving placebo ($P \leq .01$) and supported the composite ACR response analysis. The measures of the signs and symptoms of RA were not statistically better when analyses were adjusted for multiple testing.

The ACR success definition may underestimate the true effect of active treatment, since subjects who discontinued treatment prior to week 52 were then considered treatment failures even if they met the ACR response criteria. In contrast, an intent-to-treat last value carried forward analysis for improvement according to the ACR response criteria may overestimate the treatment effect because subjects can be considered responders even if they discontinue treatment because of an adverse effect. The *true* effect of active treatment is therefore intermediate between the ACR success and response rates.

The time to initial response was shorter with leflunomide treatment than with placebo or methotrexate treatment. Sustained responses occurred earlier and were of longer duration in the leflunomide group than in the placebo or methotrexate groups. An AUC analysis of the time during which an ACR response occurs offers a better estimate of clinical effect than a single time point. The mean AUC for ACR response was statistically superior for patients receiving leflunomide treatment compared with patients receiving placebo, confirming the robust clinical effect of leflunomide therapy. This response over time may best explain why leflunomide treatment resulted in significant improvement in physical function, prevention or decrease in disability, and improvement in health-related quality of life.

The primary outcome criterion for this clinical trial was improvement of 20% or greater according to the ACR response criteria, and general acceptance of this definition of improvement by rheumatologist investigators and regulatory authorities has been reaffirmed since the design and implementation of this trial. Additionally, as shown in Table 4, the ACR response rates for improvement of 50% or greater and 70% or greater compared favorably with recently published data regarding new biologic agents.[20-22] After 12 months, the leflunomide group reported an ACR response rate for improvement of 70% or greater of 20%, similar to response rates at 3 and 6 months among patients receiving 16 or 25 mg/m^2 of recombinant tumor necrosis factor receptor (p75)–Fc fusion protein (20% and 15%, respectively) or soluble tumor necrosis factor receptor (p55)–IgG protein (13%). Among patients receiving methotrexate therapy (7.5-

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15.0 mg/wk), the ACR response rate for improvement of 70% or greater was 9.4%.

Leflunomide treatment also retarded disease progression as measured by x-ray analysis. To our knowledge, this is the first 12-month placebo-controlled trial that documents a similar disease modification effect for methotrexate therapy compared with placebo.

The improvements observed in health-related quality-of-life measures are clinically meaningful. A decrease in the HAQ disability index of 0.22 is considered a minimum clinically important difference, one that is apparent to patients.[23-25] This study showed decreases of 0.45 in the leflunomide therapy group and 0.26 in the methotrexate therapy group. Minimum clinically important differences have yet to be defined for the PET questionnaire and SF-36.

In previous clinical trials of shorter duration (18 weeks to 9 months), retrospectively applied ACR response rates following methotrexate therapy of 40.3% and 64.7% have been reported compared with 8.4% for patients receiving placebo and 28.8% for patients receiving auranofin treatment, respectively.[17,26] Recently, an ACR success rate of 39% for methotrexate therapy compared with 12% for patients receiving placebo was reported in a 6-month trial that also examined cyclosporine treatment.[27,28] Several factors may account for these observed differences in response rates following methotrexate treatment: active vs placebo comparators, dosage of methotrexate administered (7.5 vs >7.5 mg/wk), and concomitant administration of folate, despite reports to the contrary.[29]

Methotrexate has become the most widely used DMARD; a recent study demonstrated that 38% of patients with RA who were receiving second-line agents received methotrexate therapy.[30] Leflunomide has a different mechanism of action than methotrexate. As a result, although adverse events commonly reported for leflunomide treatment are generally similar to those reported for methotrexate treatment administered with folate, the incidence rates of specific toxic effects differ; therefore, it is possible that patients who are unable to tolerate methotrexate therapy will be able to tolerate leflunomide therapy and vice versa. Additionally, preliminary data suggest that combination therapy with leflunomide plus methotrexate may offer benefit to patients with long-standing RA, with acceptable tolerability and no pharmacokinetic interactions.[31]

The principal adverse effects of leflunomide therapy include diarrhea, mild to moderate allergic reactions, reversible alopecia, and transaminase elevations. In this study, patients were commonly taking NSAIDs, which may have contributed to some of the gastrointestinal complaints. Oral ulcers, associated with methotrexate treatment, were less common with leflunomide treatment. As with methotrexate therapy, leflunomide therapy requires monitoring of ALT levels so that dosage adjustments can be made if necessary. Dosage reduction is recommended for repeated elevations that are greater than twice the ULN. Although data are limited, there is no evidence to suggest that leflunomide treatment is associated with the development of clinically significant liver disease. No cases of interstitial pneumonitis or renal dysfunction have been reported in patients treated with leflunomide.

As with methotrexate therapy, patients receiving leflunomide therapy must be cautioned against becoming pregnant or fathering children. Despite the long serum half-life of leflunomide, administration of cholestyramine will rapidly reduce blood levels of leflunomide in the event of an adverse event or in preparation for pregnancy.

In summary, patients receiving leflunomide therapy derived an important benefit that was demonstrated by improvement in the clinical signs and symptoms of RA;

this was first evident at 1 month and was maintained over a 1-year period, with significant retardation of disease progression confirmed by x-ray analysis and improvement in the performance of physical activities important to patients and in health-related quality of life. The results of this trial suggest that leflunomide therapy is as effective as methotrexate therapy and represents an important addition to the treatment armamentarium for patients with active RA.

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